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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/770,528	01/25/2001	Joseph A. Hedrick	DX0725K2B	7799

7590 06/05/2002

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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1646	11

DATE MAILED: 06/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/770,528	HEDRICK ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-10 and 20-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10 and 20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 January 2001 and 10 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The preliminary amendments filed 25 January 2001 (Paper No. 7) and 10 April 2002 (Paper No. 10) have been entered in full. The application is now fully in compliance with the sequence rules, 37 CFR 1.821-1.825. Claims 1-6 and 11-19 are canceled. Claims 7-10 and 20-25 are under examination.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

The disclosure is objected to because of the following informalities: There appears to be missing information at p. 31, line 31 ("xxx").

Appropriate correction is required.

Claim Objections

Claim 25 is objected to because of the following informalities: Part (5) is identical to part (8). Appropriate correction is required.

35 U.S.C. §§ 101 and 112, First Paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-10 and 20-25 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

The claims are directed to binding compounds that bind sequences from SEQ ID NO: 2, kits comprising same, compositions comprising same, methods of making antisera and methods of producing antigen:antibody complexes. The utility of the recited binding compounds lies in the polypeptide (SEQ ID NO: 2) itself. The specification asserts that the polypeptide of SEQ ID NO: 2 is a rodent IL-1δ polypeptide. The specification asserts that the invention has utility in that the IL-1δ is expected to have interleukin-1 like activities based on its structural similarity with known interleukins. For example, the specification asserts that IL-1δ can be used therapeutically for "a wide range of degenerative or abnormal conditions which directly or indirectly involve development, differentiation, or function, e.g., of the immune system and/or hematopoietic cells" (p. 3).

The assertion that the disclosed protein has biological activities similar to known IL-1 polypeptides cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual

members have distinct, and sometimes even opposite, biological activities. This is especially true for IL-1 polypeptides, as admitted in the specification at p. 3, lines 15-21, and bottom of p. 31. The ilL-1 polypeptides also bind different receptors (p. 41 of specification). Other cytokine or growth factor polypeptide families are also known in the art to have different biological activities, despite a close structural relationship. For example, Murdoch et al. (2000, Blood 95:3032-3043) reviews that chemokine receptors, which are structurally similar, are expressed on different cell types and bind different ligands such that the receptor response is highly variable (p. 3032, Abstract). Ji et al. (1998, Journal of Biological Chemistry 273:17299-17302) review the functional diversity among the structurally related G protein-coupled receptors. Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical

conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there

are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the assertion that the claimed IL-1δ cannot be accepted as credible.

If Applicant can submit evidence (in the form of a declaration under 37 CFR 1.132 or post-filing date publications) supporting the specification's assertion that the IL-1δ has a specific function, wherein the specific function was predicted by the specification as originally filed, such would be viewed favorably as evidence of patentable utility.

In view of the evidence in the art that structural similarity between soluble polypeptides like interleukins, as well as other cytokines and growth factors, cannot accurately predict functional similarity, there is no well-established utility for newly

isolated IL-1δ or the claimed binding compounds. The specification asserts several other utilities for IL-1δ; however, none of these asserted utilities meets the three-pronged test of being credible, specific and substantial. Each will be addressed in turn:

a) IL-1δ or its binding compounds can be used in therapy: This asserted utility is specific and credible, but it is not substantial. The specification provides no clear nexus between any particular disease state and any specific change in IL-1δ form or quantity. Since significant further research would be required before IL-1δ could be used in a real-world treatment of a disease, the asserted utility is not substantial.

b) IL-1δ can be used to screen for receptors, agonists or antagonists: This asserted utility is credible and substantial, but it is not specific. The same can be done with any structurally and functionally unrelated receptor.

c) IL-1δ can be used as a disease marker or as a tissue marker: The specification does not provide a nexus between any particular disease state and an alteration in forms or levels of IL-1δ. Therefore, this asserted utility is credible and specific, but it is not substantial. Significant further research would be required to discover the nexus. Use as a tissue marker is credible and substantial, but it is not specific. Numerous structurally and functionally unrelated proteins can be used as tissue markers based on their expression patterns.

d) IL-1δ can be used to make antibodies, and the antibodies can be used to identify IL-1δ: This asserted utility is credible, but not specific or substantial. Antibodies can be made from any protein. Also, there is no indication of how to use the antibodies in a real-world use.

Therefore, since the specification does not disclose a specific, substantial and credible utility for the claimed proteins, the claims are rejected under 35 U.S.C. § 101 for lack of utility.

Claims 7-10 and 20-25 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Furthermore, the specification is not enabling for the scope of the claims. Claim 7 is directed to binding compounds comprising an antigen binding site from an antibody which specifically binds a mature polypeptide comprising at least 8 contiguous amino acids from SEQ ID NO: 2. The claim does not require that the antigen binding site specifically bind the 8 contiguous amino acids. The specification does not teach nor suggest how to use binding compounds that bind sequences other than those from SEQ ID NO: 2.

Claim 10 recites formulation for oral, rectal, nasal, topical, or parenteral administration, thereby effectively reciting an intended use in therapy. Since the specification does not provide a nexus between any particular disease state and an alteration in the level or form of IL-1δ, the aspect of the claimed invention is also not enabled.

Conclusion

The claims are free of the art. The claims are not allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (703) 308-2673. The examiner can normally be reached on Mon.-Thurs. and alternate Fri., 6:30-4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D. can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elyabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

ECK
June 3, 2002